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Cellular ~~and~~ Molecular Immunology

Fifth Edition

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Chemokines involved in inflammatory reactions are produced by leukocytes in response to external stimuli, and chemokines that regulate cell traffic through tissues are produced constitutively by various cells in these tissues. The chemokines of the CC and CXC subfamilies are produced by leukocytes and by several types of tissue cells, such as endothelial cells, epithelial cells, and fibroblasts. In many of these cells, secretion of chemokines is induced by microbes and by inflammatory cytokines, mainly TNF and IL-1. Several CC chemokines are also produced by antigen-stimulated T cells, providing a link between adaptive immunity and recruitment of inflammatory leukocytes. Some chemokines are produced constitutively (i.e., without any inflammatory stimulus) in lymphoid organs, and these are involved in the physiologic traffic of lymphocytes through the organs. Chemokines of both subfamilies bind to heparan sulfate proteoglycans on endothelial cells and are displayed in this way to circulating leukocytes. In fact, the cell-associated form may be the main functional form of chemokines. The cellular display apparently provides a high local concentration of chemokines, which function to stimulate motility of leukocytes that attach to the endothelium through adhesion molecules (see Chapter 13).

Eleven distinct receptors for CC chemokines (called CCR1 through CCR11) and six for CXC chemokines (called CXCR1 through CXCR6) have already been identified, and this list is almost certainly incomplete (Fig. 11–6). Chemokine receptors are expressed on leukocytes, with the greatest number of distinct chemokine receptors seen on T cells. The receptors exhibit overlapping specificity for chemokines within each subfamily, and the pattern of cellular expression of the receptors determines which cell types respond to which chemokines. All the chemokine receptors have a characteristic structure with seven-transmembrane α-helical domains. This feature is seen in other receptors that are coupled to trimeric guanosine triphosphate (GTP)–binding proteins (G proteins), and such receptors belong to the family of G protein–coupled receptors (GPCRs). When occupied by ligand, these receptors act as GTP exchange proteins, catalyzing the replacement of bound guanosine diphosphate (GDP) by GTP. The GTP-associated form of these G proteins can activate a variety of cellular enzymes, including some that stimulate cellular locomotion. Chemokine receptors may be rapidly down-regulated by exposure to the chemokine, and this is a likely mechanism for terminating responses.

Certain chemokine receptors, notably CCR5 and CXCR4, act as coreceptors for the human immunodeficiency virus (HIV) (see Chapter 20). Some activated T lymphocytes secrete chemokines that bind to CCR5 and block infection with HIV by competing with the virus.

Biologic Actions

Chemokines were discovered on the basis of their activities as leukocyte chemoattractants, but we now know that they serve many important functions in the immune system and in other systems.

- ***Chemokines recruit the cells of host defense to sites of infection.*** Leukocyte recruitment is a result of several sequential actions of chemokines on these cells. Chemokines that are expressed on endothelial cells bound to heparan act on leukocytes rolling on the endothelium and increase the affinity of leukocyte integrins for their ligands (see Chapter 6, Fig. 6–11). This step of integrin activation is critical for the firm adherence of the leukocytes to the endothelium, as a prelude to subsequent migration into extravascular tissue. Recall that TNF and IL-1 stimulate expression of integrin ligands on endothelium, and thus these two cytokines and chemokines act cooperatively in the process of leukocyte migration. Chemokines induce movement of leukocytes and their migration toward the chemical gradient of the cytokine by stimulating alternating polymerization and depolymerization of actin filaments. Different chemokines act on different cells and thus control the nature of the inflammatory infiltrate. For instance, the CXC chemokine IL-8 recruits neutrophils preferentially, and the CC chemokine eotaxin recruits eosinophils.
- ***Chemokines regulate the traffic of lymphocytes and other leukocytes through peripheral lymphoid tissues.*** Some of the most intriguing and surprising discoveries about chemokines have been their roles in the normal migration of immune cells into lymphoid organs. In Chapter 2, we mentioned the role of different chemokines in promoting the migration of T cells, B cells, and dendritic cells to different regions of peripheral lymphoid organs (see Fig. 2–11, Chapter 2). Various chemokines also promote migration of previously activated effector and memory T cells to nonlymphoid tissues, including mucosal organs and skin. The selectivity of different cell types for different tissues depends to a large extent on which chemokines are produced in the tissues and which chemokine receptors are expressed on the cell types.
- Chemokines are also involved in the development of diverse nonlymphoid organs. Knockout mice lacking the CXCR4 receptor have fatal defects in the development of the heart and the cerebellum. These roles of chemokines are unexpected and raise the possibility of many other as yet undiscovered functions in morphogenesis.

Interleukin-12 (IL-12)

IL-12 is a principal mediator of the early innate immune response to intracellular microbes and is a key inducer of cell-mediated immunity, the adaptive immune response to these microbes. IL-12 was originally identified as an activator of NK cell cytolytic function, but its most important action is to stimulate IFN-γ production by T cells as well as by NK cells.